

Figure 1

An amino acid sequence of human, type I, IMPDH protein

IMPDH = INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE 1
, 514 residues

MADYLISGGT GYVPEDGLTA QQLFASADDL TYNDFLILPG FIDFIADEV
LTSALTRKIT LKTPLISSPM DTVTEADMAI AMALMGGIGF IHHNCTPEFQ
ANEVRKVKNF EQGFITDPVV LSPSHTVGDV LEAKMRHGFS GIPITETGTM
GSKLVGIVTS RDIDFLAEKD HTTLLSEVMT PRIELVVAPA GVTLKEANEI
LQRSKKGKLP IVNDCDELVA IIARTDLKKN RDYPLASKDS QKQLLCGAAV
GTREDDKYRL DLLTQAGVDV IVLDSSQGNS VYQIAMVHYI KQKYPHLQVI
GGNVVTAAQA KNLIDAGVDG LRVGMGCGSI CITQEVMACG RPQGTAVYKV
AEYARRFGVP IIADGGIQT V GHVVKALALG ASTVMMGSL AATTEAPGEY
FFSDGVRLKK YRGMGSLDAM EKSSSSQKRY FSEGDKVKIA QGVSGSIQDK
GSIQKFVPYL IAGIQHGCQD IGARSLSVLR SMMYSGELKF EKRTMSAQIE
GGVHGLHSYE KRLY

0055918-01004

Figure 2

An amino acid sequence of human, type II IMPDH protein

IMPDH = INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE 2
, 514 residues

The underlined region correlates with the subdomain region

MADYLISGGT SYVPDDGLTA QQLFNCGDGL TYNDFLILPG YIDFTADQVD
LTSALTKKIT LKTPLVSSPM DTVTEAGMAI AMALTGGIGF IHHNCTPEFQ
ANEVRKVKKY EQGFITDPVV LSPKDRVRDV FEAARHGFC GIPITDTGRM
GSRLVGIISS RDIDFLKEEE HDCFLEEIMT KREDLVVAPA GITLKEANEI
LQRSKKGKLP IVNEDDELVA IIARTDLKKN RDYPLASKDA KKQLLCGAAI
GTHEDDKYRL DLLAQAGVDV VVLDSSQGNS IFQINMIKYI KDKYPNLQVI
GGNVVTAAQA KNLIDAGVDA LRVGMGSGSI CITQEVLAGC RPQATAVYKV
SEYARRFGVP VIADGGIQNV GHIKALALG ASTVMMGSLI AATTEAPGEY
FFSDGIRLKK YRGMGSLDAM DKHLSSQNRV FSEADKIKVA QGVSGAVQDK
GSIHKFVPYL IAGIQHSCQD IGAKSLTQVR AMMYSGELKF EKRTSSAQVE
GGVHSLHSYE KRLF

09653918-051001

FIGURE 3
The Subdomain of Wild-Type, Human, and Type II
IMPDH is Replaced with an Oligo-Peptide

Met-1	Tyr-110	Leu-243	Phe-514
	oligo		
	peptide		

Figure 4

The amino acid sequence of the modified IMPDH-DKT polypeptide 384 residues.

The substitute tri-peptide DKT sequence is highlighted in bold print

MADYLISGGT SYVPDDGLTA QQLFNCGDGL TYNDFLILPG YIDFTADQVD
LTSALTKKIT LKTPLVSSPM DTVTEAGMAI AMALTGGIGF IHHNCTPEFQ
ANEVRKVKKY **DKT**LLCGAAI GTHEDDKYRL DLLAQAGVDV VVLDSSQGNS
IFQINMIKYI KDKYPNLQVI GGNVVTAQA KNLIDAGVDA LRVGMGSGSI
CITQEVLAGG RPQATAVYKV SEYARREGVP VIADGGIQNV GHIKALALG
ASTVMMGSLA AATTEAPGEY FFSDGIRLKK YRGMGSLDAM DKHLSSQNRY
FSEADKIKVA QGVSGAVQDK GSIHKFVPYL IAGIQHSCQD IGAKSLTQVR
AMMYSGELKF EKRTSSAQVE GGVHSLHSYE KRLF

095918-051004

Figure 5

The nucleotide sequence of type II, IMPDH-DKT cDNA

atggccgactacctgattagtgggggcacgtcctacgtgccagacgacggactcacagcacagcagctct
tcaactgcgagacggcctcacctacaatgactttctcattctccctgggtacatcgacttcactgcaga
ccaggtggacctgacttctgctctgaccaagaaaatcactcttaagaccccactggtttctctccatg
gacacagtcacagaggtgggatggcatagcaatggcgcttacaggcggtattggcttcaccaccaca
actgtacacctgaattccaggccaatgaagttcggaaagtgaagaaatatgacaagacctgctgtgtgg
ggcagccattggcactcatgaggatgacaagtataggctggacttgctcgccaggctgggtgtggatgta
gtgggtttggactcttcccagggaattccatctccagatcaatatgatcaagtacatcaaagacaaat
accctaattctcaaagtcattggaggcaatgtggtcactgctgccaggccaagaacctcattgatgcagg
tgtggatgcccctgcgggtgggcatgggaagtggctccatctgcattacgcaggaagtgtggcctgtggg
cgcccccaagcaacagcagtgtagaaggtgtcagagtatgcacggcgctttgggtgttcgggtcattgctg
atggaggaatccaaaatgtgggtcatattgcgaaagccttggcccttggggcctccacagtcattgatggg
ctctctcctggctgccaccactgaggccctgggtgaatacttcttttccgatgggatccggctaaagaaa
tategcggtatgggttctctcgatgccatggacaagcacctcagcagccagaacagatatttcagtgaag
ctgacaaaatcaaagtggcccaggagtggtctggtgctgtgcaggacaaagggccaatccacaaatttgt
cccttacctgattgctggcatccaactcatgccaggacattgggtgccaagagcttgacccaagtcgga
gccatgatgtactctggggagcttaagtttgagaagagaacgtcctcagcccagggtggaaggtggcgtcc
atagcctccattcgtatgagaagcggcttttctga

055348-051004

Figure 6

The amino acid sequence of the modified IMPDH-SPS
polypeptide 384 residues.

The substitute tri-peptide SPT sequence is highlighted in
bold print.

MADYLISGGT SYVPDDGLTA QQLFNCGDGL TYNDFLILPG YIDFTADQVD
LTSALT¹TKKIT LKTPLVSSPM DTVTEAGMAI AMALTGGIGF IHHNCTPEFQ
ANEV²RKVKKY **SPS**LLCGAAI GTHEDDKYRL DLLAQAGVDV VVLDSSQGNS
IFQINMIKYI KDKYPNLQVI GGNVV³TAAQA KNLIDAGVDA LRVGMGSGSI
CITQEVLACG RPQATAVYKV SEYARRFGVP VIADGGIQNV GHIAKALALG
ASTVMMGSL⁴L AATTEAPGEY FFSDGIRLKK YRGMGSLDAM DKHLSSQNRY
FSEADKIKVA QGVSGAVQDK GSIHKFVPYL IAGIQHSCQD IGAKSLTQVR
AMMYSGELKF EKRTSSAQVE GGVHSLHSYE KRLF

09594-05100
T00T50-BT6E5850

FIGURE 7

The nucleotide sequence of type II, IMPDH-SPS cDNA

atggccgactacctgattagtgggggcacgtcctacgtgccagacgacggactcacagcacagcagctct
tcaactgcgagacggcctcacctacaatgactttctcattctccctgggtacatcgacttcactgcaga
ccaggtggacctgacttctgctctgaccaagaaaatcactcttaagacccactggtttcctctcccatg
gacacagtcacagaggtgggatggccatagcaatggcgcttacaggcggtattggcttcacaccaca
actgtacacctgaattccaggccaatgaagttcggaaaagtgaagaaatattctccgagcctgctgtgtgg
ggcagccattggcactcatgaggatgacaagtataggctggacttgctcgcccaggctgggtgtggatgta
gtgggttttggactcttcccagggaattccatcttcagatcaatatgatcaagtacatcaaagacaaat
accctaattctcaaagtcattggaggcaatgtggtcactgctgccaggccaagaacctcattgatgcagg
tgtggatgccctgcggtgggcatgggaagtggctccatctgcattacgcaggaagtgtggcctgtggg
cgcccccaagcaacagcagtgtaacaaggtgtcagagtatgcacggcgctttgggtgttcgggtcattgctg
atggaggaatccaaaatgtgggtcatattgcgaaagccttggcccttggggcctccacagtcattgatggg
ctctctcctggctgccaccactgaggccctgggaatacttcttttcgatgggatccggctaaagaaa
tatcgcggtatgggttctctcgatgccatggacaagcacctcagcagccagaacagatatttcagtgaag
ctgacaaaatcaaagtggcccagggaagtgtctggtgctgtgcaggacaaaggtcaatccacaaatttgt
cccttacctgattgctggcatccaacactcatgccaggacattgggtgccaaagagcttgacccaagtcgga
gccatgatgtactctggggagcttaagtttgagaagagaaacgtcctcagcccagggtggaaggtggcgctcc
atagcctccattcgatgagaagcggcttttctga

10985438.054001

Figure 8

The amino acid sequence of the type II, modified IMPDH-GSG polypeptide

The substitute tri-peptide GSG sequence is highlighted in bold print

MADYLISGGT SYVPDDGLTA QQLFNCGDGL TYNDFLILPG YIDFTADQVD
LTSALTKKIT LKTPLVSSPM DTVTEAGMAI AMALTGGIGF IHHNCTPEFQ
ANEVRKVKKY **GSG**LLCGAAI GTHEDDKYRL DLLAQAGVDV VVLDSSQGNS
IFQINMIKYI KDKYPNLQVI GGNVVTAAQA KNLIDAGVDA LRVGMGSGSI
CITQEVLAGC RPQATAVYKV SEYARRFGVP VIADGGIQNV GHIKALALG
ASTVMMGSLI AATTEAPGEY FFSDGIRLKK YRGMGSLDAM DKHLSSQNRY
FSEADKIKVA QGVSGAVQDK GSIHKFVPYL IAGIQHSCQD IGAKSLTQVR
AMMYSGELKF EKRTSSAQVE GGVHSLHSYE KRLF

100T50-8T65850

Figure 9

The nucleotide sequence of type II, IMPDH-GSG cDNA

atggccgactacctgattagtgggggcacgtcctacgtgccagacgacggactcacagcacagcagctct
tcaactgcgagacggcctcacctacaatgactttctcattctccctgggtacatcgacttcactgcaga
ccaggtggacctgacttctgctctgaccaagaaaatcactcttaagacccactggtttctctcccatg
gacacagtcacagaggctgggatggccatagcaatggcgcttacaggcggtattggcttcaccaccaca
actgtacacctgaattccaggccaatgaagttcggaagtgagaaatattggttccggcctgctgtgtgg
ggcagccattggcactcatgaggatgacaagtataggctggacttgctcgccaggctggtgtggatgta
gtggttttggactcttcccagggaattccatcttcagatcaatatgatcaagtacatcaaagacaaat
accctaattctccaagtcattggaggcaatgtggtcactgctgccaggccaagaacctcattgatgcagg
tgtggatgccctgcggtgggcatgggaagtggctccatctgcattacgcaggaagtgtggcctgtggg
cgcccccaagcaacagcagtgtagaaggtgtcagagtatgcacggcgctttggtgttccggctcattgctg
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ctctctcctggctgccaccactgaggcccctggtgaatacttcttttccgatgggatccggctaaagaaa
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ctgacaaaatcaaagtggcccagggaagtgtctggtgctgtgcaggacaaagggtaatccacaaatttgt
cccttacctgattgctggcatccaacactcatgccaggacattggtgccaagagcttgacccaagtccga
gccatgatgtactctggggagcttaagtttgagaagagaaogtccctcagcccagggtggaaggtggcgctc
atagcctccattcgatgagaagcggttttctga

095918-051001

Figure 10

The amino acid sequence of the modified IMPDH-SPT polypeptide 384 residues.

The substitute tri-peptide SPT sequence is highlighted in bold print.

MADYLISGGT SYVPDDGLTA QQLFNCGDGL TYNDFLILPG YIDFTADQVD
LTSALT¹TKKIT LKTPLVSSPM DTVTEAGMAI AMALTGGIGF IHHNCTPEFQ
ANEVRKVKKY **SPT**LLCGAAI GTHEDDKYRL DLLAQAGVDV VVLDSSQGNS
IFQINMIKYI KDKYPNLQVI GGNVVTAQA KNLIDAGVDA LRVGMGSGSI
CITQEVLAGG RPQATAVYKV SEYARREGVP VIADGGIQNV GHIKALALG
ASTVMMGSLA AATTEAPGEY FFSDGIRLKK YRGMGSLDAM DKHLSSQNRY
FSEADKIKVA QGVSGAVQDK GSIHKFVPYL IAGIQHSCQD IGAKSLTQVR
AMMYSGELKF EKRTSSAQVE GGVHSLHSYE KRLF

095318.051001

Figure 11

The nucleotide sequence of type II, IMPDH-SPT cDNA

atggccgactacctgattagtgggggcacgtcctacgtgccagacgacggactcacagcacagcagctct
tcaactgcgagacggcctcacctacaatgactttctcattctccctgggtacatcgacttcactgcaga
ccaggtggacctgacttctgctctgaccaagaaaatcactcttaagaccccactggtttctctccatg
gacacagtcacagaggctgggatggccatagcaatggcgcttacaggcggtattggcttcacccaca
actgtacacctgaattccaggccaatgaagttcggaagtgaagaaatattctcogactctgctgtgtgg
ggcagccattggcactcatgaggatgacaagtataggctggacttgctcgccaggtggtgtggatgta
gtggttttggactcttcccagggaattccatcttccagatcaatatgatcaagtacatcaaagacaaat
accctaattctcaagtcattggaggcaatgtggtcactgctgcccaggccaagaacctcattgatgcagg
tgtggatgccctgccccgggcatgggaagtggctccatctgcattacgcaggaagtgtgtggctgtggg
cgcccccaagcaacagcagtgataaggtgtcagagtatgcacggcgctttgggtgttcgggtcattgctg
atggaggaatccaaaatgtgggtcatattgcgaaagccttggcccttggggcctccacagtcattgctg
ctctctcctggctgccaccactgaggccccctggtgaatacttctttccgatgggatccggctaaagaaa
tatcgcggtatgggttctctcgatgccatggacaagcacctcagcagccagaacagatatttcagtgaag
ctgacaaaatcaaagtggcccaggagtgctgtgtgtgcaggacaaagggccaatccacaaatttgt
cccttacctgattgctggcatccaacactcatgccaggacattggtgccaagagcttgacccaagtccga
gccatgatgtactctggggagcttaagtttgagaagagaacgtcctcagcccagggtggaaggtggcgctc
atagcctccattcgatgagaagcggcttttctga

100750 8158560

Figure 12

The nucleotide sequence of type II, IMPDH-SPTQ cDNA

atggccgactacctgattagtgggggcacgtcctacgtgccagacgacggactcacagcacagcagctct
tcaactgctggagacggcctcacctacaatgactttctcattctccctgggtacatcgacttcactgcaga
ccaggtggacctgacttctgctctgaccaagaaaatcactcttaagaccccactgggttctctcccatg
gacacagtacagaggctgggatggccatagcaatggcgcttacaggcggtattggcttcatccaccaca
actgtacacctgaattccaggccaatgaagttcggaaagtgaagaaatattctccgactcagctgctgtg
tggggcagccattggcactcatgaggatgacaagtataggctggacttgcctgccaggctgggtgtggat
gtagtgggttttggactcttcccagggaattccatcttccagatcaatatgatcaagtacatcaaagaca
aataccctaatctccaagtcattggaggcaatgtggtcactgctgccaggccaagaacctcattgatgc
aggtgtggatgcctgcgggtgggcatgggaagtggctccatctgcattacgcaggaagtgtggcctgt
ggcgggccccaagcaacagcagtgtaaaagtgtcagagtatgcacggcgctttgggtgttccggctcattg
ctgatggaggaatccaaaatgtgggtcatattgcgaaagccttggcccttggggcctccacagtcattg
gggtctctcctggctgccaccactgaggccctgggtgaatacttcttttccgatgggatccggctaaag
aaatatcgcggtatgggttctctcgatgccatggacaagcacctcagcagccagaacagatatattcagtg
aagctgacaaaatcaaagtggcccaggagtgctgtggtgctgtgcaggacaaagggtaaatccacaaatt
tgtccttacctgattgctggcatccaactcatgccaggacattgggtgccaagagcttgacccaagtc
cgagccatgatgtactctggggagcttaagtttgagaagagaacgtcctcagcccagggtggaaggtggcg
tccatagcctccattcgtatgagaagcggcttttctga

100150151525354555657585960

Figure 13

The amino acid sequence of the modified type II, IMPDH-AGRP polypeptide
385 residues

The substitute tetra-peptide AGRP sequence is highlighted
in bold print.

MADYLI¹SGGT SYVPDDGLTA QQLFNCGDGL TYNDFLILPG YIDFTADQVD
LTSALTKKIT' LKTPLVSSPM DTVTEAGMAI AMALTGGIGF IHHNCTPEFQ
ANEVRKVKKY **AGRP**LLCGAA IGTHEDDKYR LDLLAQAGVD VVVLDSQGN
SIFQINMIKY IKDKYPNLQV IGGNVVTAAQ AKNLIDAGVD ALRVGMGSGS
ICITQEVLAC GRPQATAVYK VSEYARRFGV PVIADGGIQN VGHIAKALAL
GASTVMMGSL LAATTEAPGE YFFSDGIRLK KYRGMGSLDA MDKHLSSQNR
YFSEADKIKV AQGVSGAVQD KGSIHKFVPY LIAGIQHSCQ DIGAKSLTQV
RAMMYSGELK FEKRTSSAQV EGGVHSLHSY EKRLF

0985918 05400
T00750 816580

Figure 14

The nucleotide sequence of type II, IMPDH-AGRP

atggccgactacctgattagtgggggcacgtcctacgtgccagacgacggactcacagcacagcagctct
tcaaetgcgagacggcctcacctacaatgactttctcattctccctgggtacatcgacttcaactgcaga
ccaggtggacctgacttctgctctgaccaagaaaatcactcttaagacccactggtttctctccatg
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tggggcagccattggcactcatgaggatgacaagtataggctggacttgctcgcccaggctgggtgtggat
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ctgatggaggaatccaaaatgtgggtcatattgcgaaagccttggcccttggggcctccacagtcattgat
gggctctctcctggctgccaccactgaggccctggtgaatacttcttttccgatgggatccggctaaag
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aagctgacaaaatcaaagtggcccaggagtgctggtgctgtgcaggacaaaggtcaatccacaaatt
tgtcccttacctgattgctggcatccaacactcatgccaggacattggtgccaagagcttgacccaagtc
cgagccatgatgtactctggggagcttaagtttgagaagagaacgtcctcagcccagggtggaaggtggcg
tccatagcctccattcgtatgagaagcggcttttctga

095918-051001

Figure 15

The amino acid sequence of type II, modified IMPDH-NSPL polypeptide

The substitute tri-peptide is highlighted in bold print

MADYLI\$GGT SYVPDDGLTA QQLFNCGDGL TYNDFLILPG YIDFTADQVD
LTSALTKKIT LKTPLVSSPM DTVTEAGMAI AMALTGGIGF IHHNCTPEFQ
ANEVRKVKKY **NSPL**LLCGAA IGTHEDDKYR LDLLAQAGVD VVVLDSQGN
SIFQINMIKY IKDKYPNLQV IGGNVVTAAQ AKNLIDAGVD ALRVGMGSGS
ICITQEV LAC GRPQATAVYK VSEYARRFGV PVIADGGIQN VGHIKALAL
GASTVMMGSL LAATTEAPGE YFFSDGIRLK KYRGMGSLDA MDKHLSSQNR
YFSEADKIKV AQGVSGAVQD KGSIHKEVPY LIAGIQHSCQ DIGAKSLTQV
RAMMYSGELK FEKRTSSAQV EGGVHSLHSY EKRLF

095318-05100
T00T50-87E586

Figure 16

The nucleotide sequence of type II, IMPDH-NSPL cDNA

atggccgactacctgattagtgggggcacgtcctacgtgccagacgacggactcacagcacagcagctct
tcaactgcgagacggcctcacctacaatgactttctcattctccctgggtacatcgacttcaactgcaga
ccaggtggacctgacttctgctctgaccaagaaaatcactcttaagacccactggtttctctcccatg
gacacagtcacagaggctgggatggccatagcaatggcgcttacaggcggtattggcttcatccaccaca
actgtacacctgaattccaggccaatgaagttcggaaagtgaagaaatataactctccgcttctgctgtg
tggggcagccattggcactcatgaggatgacaagtataggctggacttgctcgcccaggctgggtgtggat
gtagtggttttggactcttcccagggaattccatcttccagatcaatatgatcaagtacatcaaagaca
aataccctaattctccaagtcattggaggcaatgtggtcactgctgccaggccaagaacctcattgatgc
aggtgtggtatgcctgcggtgggcatgggaagtggctccatctgcattacgcaggaagtgtggcctgt
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ctgatggaggaatccaaaatgtgggtcatattgcgaaagccttggcccttggggcctccacagtcattg
gggctctctcctggctgccaccactgaggcccttgggaatacttcttttccgatgggatccggctaaag
aaatatcgcggtatgggttctctcgatgccatggacaagcacctcagcagccagaacagatatttcagt
aagctgacaaaatcaaagtggcccaggagtgctgtggtgctgtgcaggacaaagggtcaatccacaaatt
tgtcccttacctgattgctggcatccaactcatgccaggacattgggtgccaagagcttgacccaagtc
cgagccatgatgtactctggggagcttaagtttgagaagagaacgtcctcagcccagggtggaagggtggcg
tccatagcctccattcgatgagaagcggttttctga

09853918-051001

Figure 17

The amino acid sequence of the type I modified IMPDH-DKT polypeptide

The substitute tri-peptide DKT is highlighted in bold print

MADYLISGGT GYVPEDGLTA QQLFASADGL TYNDFLILPG FIDFIADDEV
LTSALTRKIT LKTPLISSPM DTVTEADMAI AMALMGGIGF IHHNCTPEFQ
ANEVRKVKKF **DKT**LLCGAAV GTREDDKYRL DLLTQAGVDV IVLDSSQGNS
VYQIAMVHYI KQKYPHLQVI GGNVVTAQA KNLIDAGVDG LRVGMGCGSI
CITQEVMACG RPQGTAVYKV AEYARRFGVP IIADGGIQT V GHVVKALALG
ASTVMMGSL AATTEAPGEY FFSDGVRLKK YRGMGSLDAM EKSSSSQKRY
FSEGDKVKIA QGVSGSIQDK GSIQKFVPYL IAGIQHGCQD IGARSLSVLR
SMMYSGELKF EKRTMSAQIE GGVHGLHSYE KRLY

09653918-051001

Figure 18

A schematic representation of the distance that the substitute oligo-peptides are designed to span in a folded modified IMPDH polypeptide.

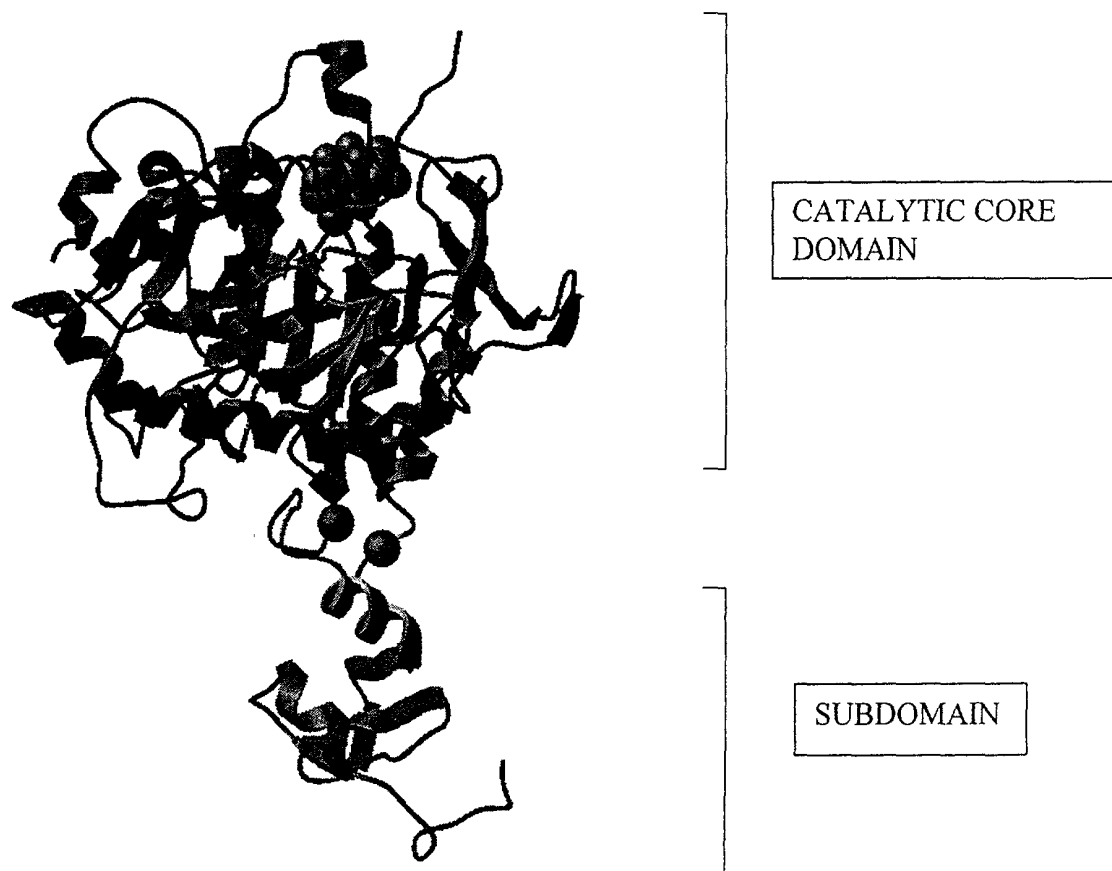


Figure 19

The Rate of NADH Production at 37 °C for Wild-Type IMPDH (type II) and Various Modified IMPDH Multimers.

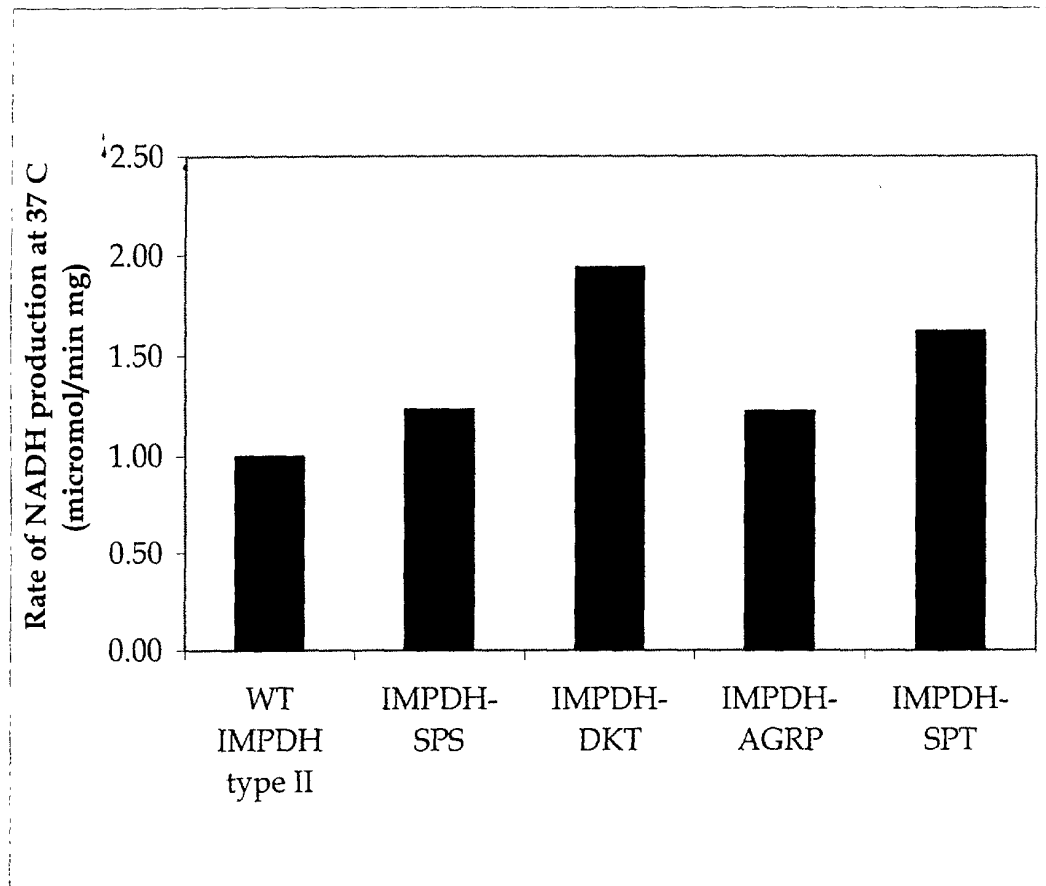
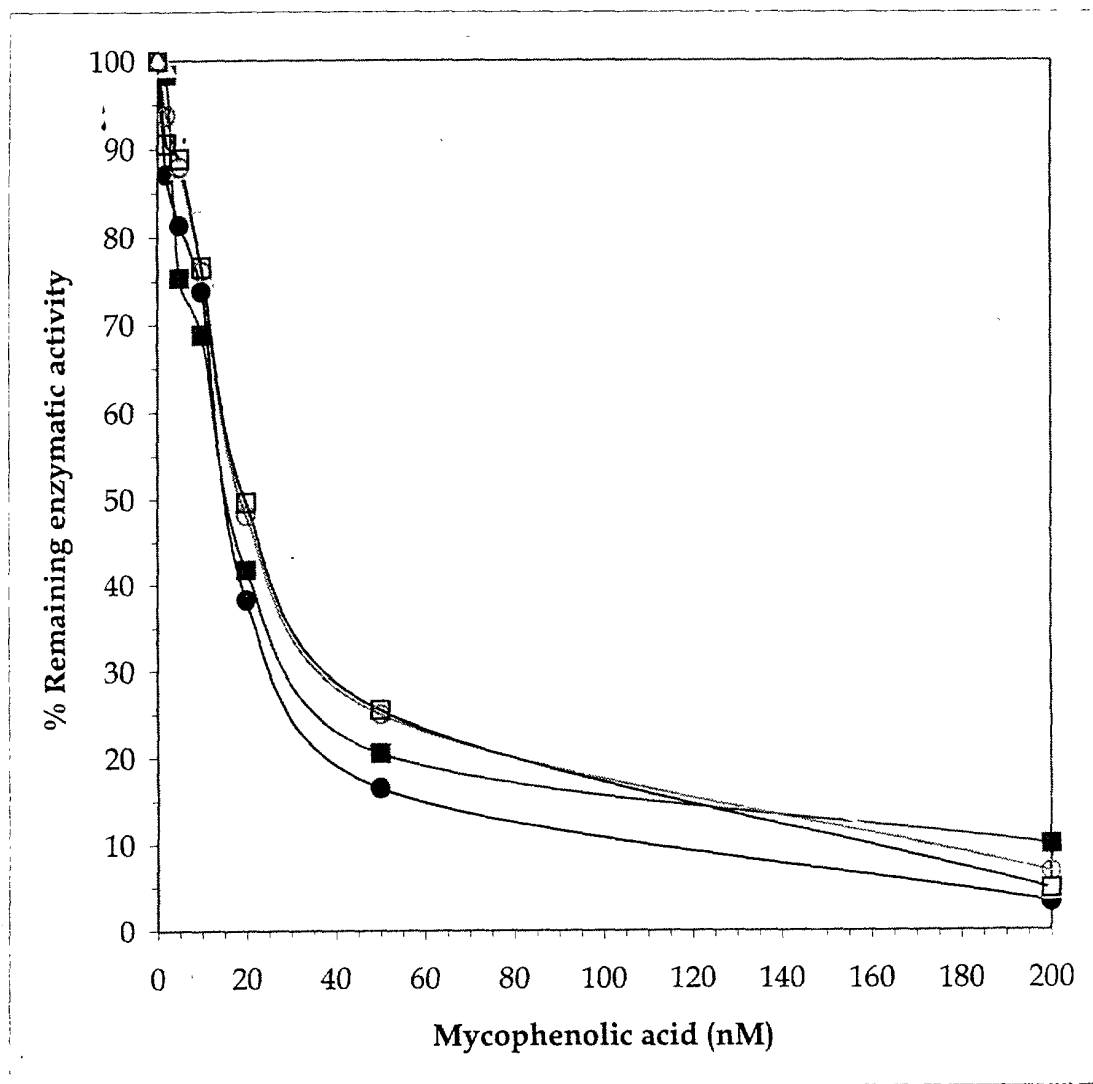


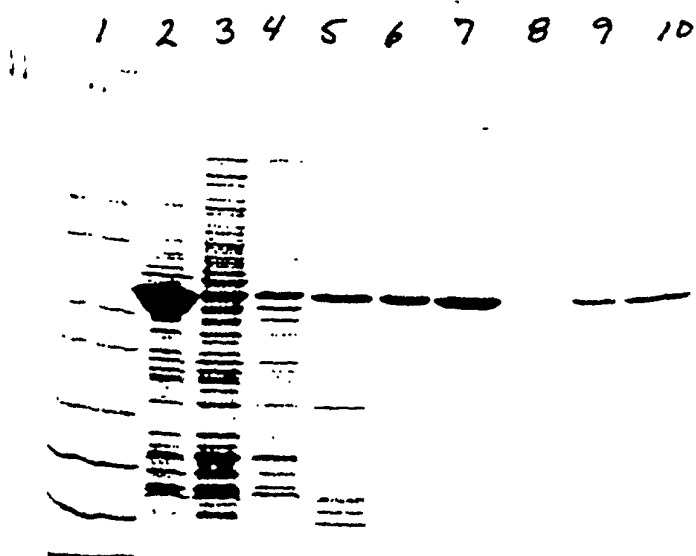
Figure 20

MPA Inhibits the Activity of Various Modified IMPDH Polypeptides.



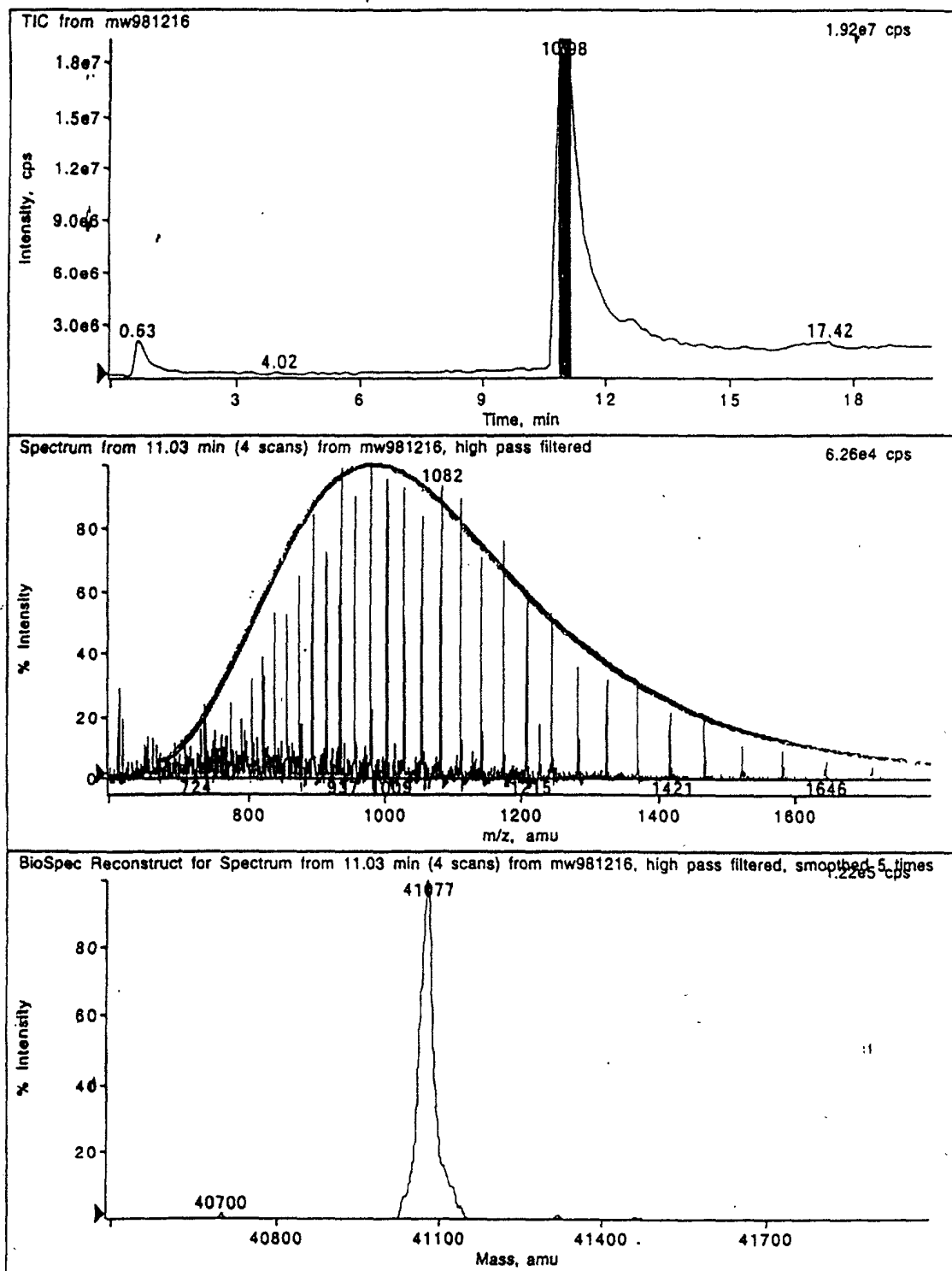
- wild-type, type II IMPDH
- type II, IMPDH-AGRP
- type II, IMPDH-SPS
- type II, IMPDH-SPT
- ▲ type II, IMPDH-DKT

FIGURE 21



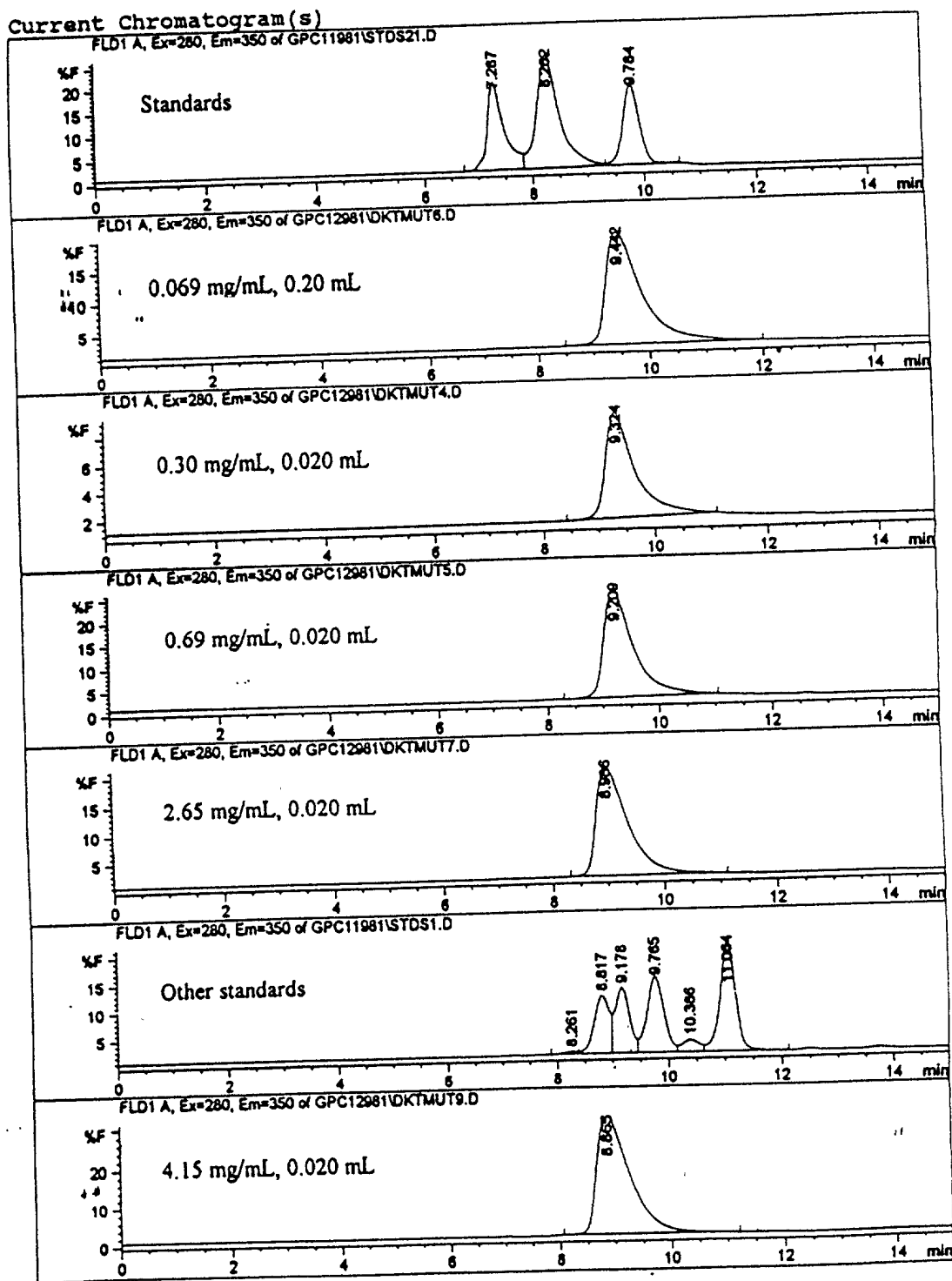
- Lane #
- 1: Novex standards (25 μ L)
 - 2: Total cell lysate (1 μ L, 12 μ g; before ultracentrifugation)
 - 3: Soluble lysate (2.5 μ L, 10 μ g; after 100,000 \times g, 1 hr, 4 $^{\circ}$ C)
 - 4: Unbound AE sample (13 μ L, \sim 10 μ g)
 - 5: Blue dye column, frs. #32-70 (25 μ L, 4.5 μ g)
 - 6: IMP affinity column, IMP eluted (10 μ L, \sim 1.5 μ g)
 - 7: IMP affinity column, IMP eluted (20 μ L, \sim 3.0 μ g)
 - 8: Unbound protein to IMP column (25 μ L, \sim 2.0 μ g)
 - 9: IMP affinity column (from AE fr. #1-10, 10 μ L, 1.2 μ g)
 - 10: IMP affinity column (from AE fr. #1-10, 25 μ L, 3.0 μ g)

FIGURE 22



T00T50-8T65850

FIGURE 23



FOOTPRINT 8765860

The nucleotide sequence of type I, IMPDH-DKT

[illegible]